Detailed cadaveric analysis of perivesical lymph nodes in cystectomy specimens

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Introduction: *Perivesical lymph nodes were added to the 8th edition of American Joint Committee on Cancer (AJCC) staging for bladder cancer. Currently, these nodes are inconsistently evaluated at the time of radical cystectomy. The objective of this study was to provide a detailed anatomic evaluation of perivesical lymph nodes.*

Materials and methods: *A radical cystectomy was performed on six un-embalmed cadavers with wide resection of perivesical tissue and meticulous care to separate the pelvic sidewall lymph nodes (e.g. obturator, external iliac) from the bladder and perivesical en-bloc specimen. Perivesical tissue dissection in 2 mm slices was performed with a board-certified pathologist. Lymph node size and location were recorded.*

Results: *Gross tissue resembling lymph nodes were identified in the perivesical tissue in 50% (3/6) of the specimens, with a total of six grossly identified lymph nodes. The mean size was 7.5 mm (2-16 mm). On histologic analysis, 4 of 6 (66%) putative gross lymph nodes had confirmed lymphoid tissue. The mean distance of the lymph nodes from bladder wall was 9 mm (3-15 mm). Eight anatomic locations for perivesical nodes were developed: urachal, anterior bladder wall, posterior peritoneum, bladder neck, bilateral pedicle, bilateral lateral bladder wall.*

Conclusion: *This cadaveric study with meticulous dissection of the perivesical space confirms that perivesical lymph nodes are a distinct entity and separate from other lymph nodes in the true pelvis. Perivesical lymph nodes are not present in all subjects and pathologic evaluation is more difficult owing to the surrounding fat. We herein propose perivesical regions for evaluation which can serve as a foundation for future studies and anatomic grossing techniques.*

Key Words: bladder cancer, lymph nodes, TNM staging, lymphatic metastasis, cystectomy

Introduction

Radical cystectomy is the standard of care for patients with localized, muscle-invasive bladder cancer and is an option for patients with high-risk, non-muscle invasive bladder cancer. Pelvic lymph node dissection performed at time of radical cystectomy is recommended in patients with urothelial carcinoma of the bladder as it has proven survival benefits and provides important prognostic information.[1-3]

The extent of lymph node dissection is controversial.[4,5] Most studies have evaluated the benefit of extending the cephalad limit of the lymphadenectomy.[6] Prospective, randomized clinical trials such as SWOG-1011 (NCT01224665), are evaluating the survival benefit of an extended lymphadenectomy or super-extended lymphadenectomy excising the common iliac and retroperitoneal lymph nodes, respectively.

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However, a recent study has demonstrated a previously under-recognized implication of positive lymph nodes in the perivesical tissue.[7] In patients with confirmed nodal metastasis, positive perivesical lymph nodes were associated with worse overall survival even when adjusting for the number of positive lymph nodes. Therefore, assessment for perivesical nodes within the cystectomy specimen has been proposed to better stage patients. This effort has been reflected in the 8th edition of the American Joint Committee on Cancer (AJCC) staging for bladder cancer, which has classified perivesical lymph nodes as N1 disease.[8]

Despite the prognostic value of perivesical node examination, these nodes can be inconsistently defined and evaluated at the time of radical cystectomy. Most importantly, there is no clear definition of what constitutes a perivesical lymph node. From the surgical perspective, defining the nodes can be problematic as there is variation in how surgeons send pelvic lymph node packets. Some excise lymph nodes en-bloc with the bladder specimen and while others send them in separate anatomic packets. The lymph node mapping in anatomic packets can be dependent upon surgeon discretion with inherent variability. Evaluation of perivesical nodes from the pathologic perspective can be unclear if these nodes are anatomically distinct from the adjacent nodes such as the external iliac or obturator/hypogastric lymph nodes.

From an anatomic grossing perspective, close attention to the presence or pathologic involvement of perivesical lymph nodes can vary. The cystectomy specimen is evaluated closely for the extent of the primary tumor, additional urothelial lesions, and surgical margin status. Given the relatively new emphasis of perivesical lymph nodes, close evaluation of the perivesical tissue may not be standard practice, especially across the spectrum of pathology departments that may not have dedicated genitourinary pathologists. Compounding this issue is that lymph nodes can, at times, be very small and have similar appearance and texture to perivesical fat. Lastly, there can be discrepancies between gross and microscopic evaluation. Performing a detailed evaluation of the perivesical tissue in pathologic practice can be difficult due to the intensity of work as well as costs related to sending tissue for microscopic analysis.

Given the potential oncologic importance of perivesical lymph nodes yet wide variability in their pathologic definition and evaluation, we sought to perform a detailed anatomic study. This study aimed to define their presence, incidence, and location in relation to the bladder. With this information, anatomic perivesical zones are proposed to standardize identification and reporting.

Materials and methods

Cadaver parameters

Six un-embalmed cadavers were utilized for this study, including four male and two female cadavers. Selection criteria included cadavers with no prior bladder malignancy, no prior prostate malignancy, no prior pelvic malignancy, and no prior pelvic surgery. Exclusion criteria was age < 18 years, and presence of a low abdominal or pelvic scar.

Specimen extraction

An open radical cystectomy was performed on all specimens with en-bloc wide resection of perivesical tissue, Figure 1A. In female cadavers, the anterior vagina was resected en-bloc with the bladder. During dissection, meticulous care was taken to separate the pelvic sidewall lymph nodes (e.g. obturator, external iliac) from the specimen. The cystectomy was performed with a Society of Urologic Oncology fellowship-trained urologic oncologist.

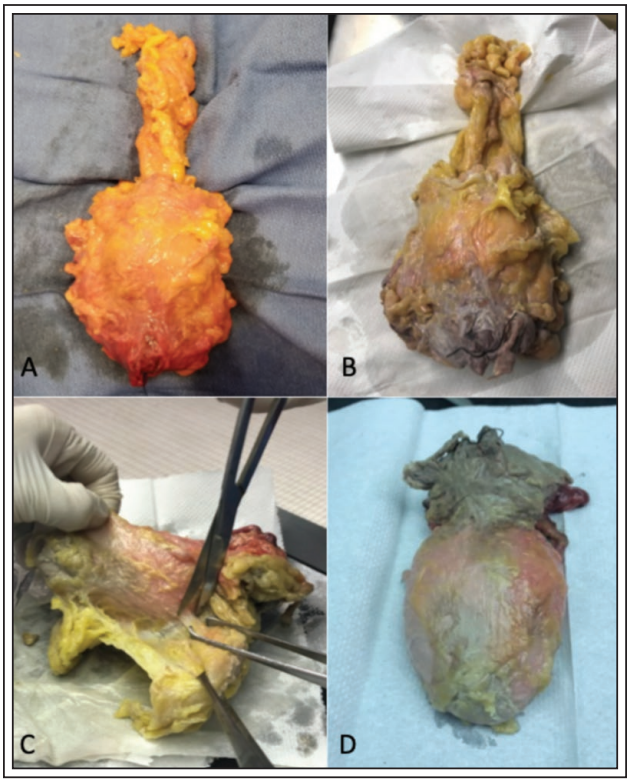

Figure 1. A) Open radical cystectomy approach with en-bloc wide resection of perivesical tissue. **B)** Specimen after fixation using lymph node revealing solution for 6 hours. **C)** Perivesical tissue dissection performed with a board-certified pathologist. **D)** Bladder specimen after perivesical lymph node dissection.

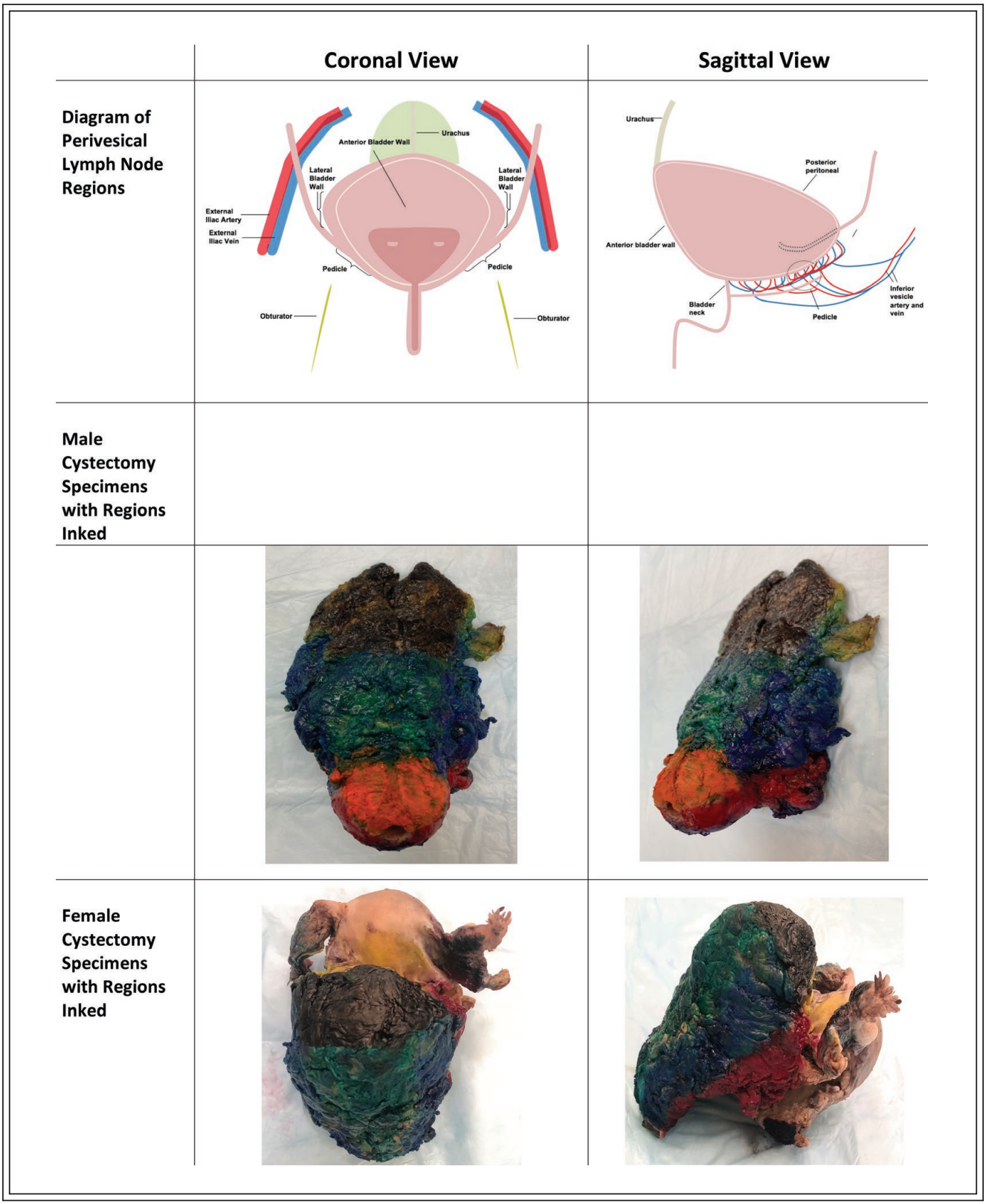

Figure 2. Illustration of proposed perivesical regions and inked specimens based on perivesical region in the coronal and sagittal planes.

TABLE 1. **Perivesical regions for gross and histologically-confirmed lymph nodes**

Location	Number of grossly identified/histologically-confirmed nodes					
	Cadaver 1 (Male)	Cadaver 2 (Male)	Cadaver 3 (Male)	Cadaver 4 (Female)	Cadaver 5 (Female)	Cadaver 6 (Male)
Urachal	-	-	-	-	-	-
Anterior bladder wall	-	1 / 0	-	-	-	-
Posterior peritoneum	-	1 / 0	-	-	-	-
Bladder neck	-	-	-	-	-	-
Left peri-pedicle	-	-	-	-	-	-
Right peri-pedicle	2 / 2	-	-	-	-	-
Left lateral bladder wall		-	-	-	-	2/2
Right lateral bladder wall	-	-	-	-	-	-

Perivesical lymph node fixation and pathologic examination

The bladder specimens including perivesical tissue were fixed in previous validated lymph node revealing solution for 6 hours, Figure 1B. The solution is comprised 95% ethanol, diethyl ether, glacial acetic acid and buffered formalin (65:20:5:10 ratio) prepared under a fume-hood. This methodology differs from the majority of studies to date evaluating lymph node counts in the pelvis that have relied primarily upon manual palpation. The abundance of perivesical fat necessitated using this solution that acts to desiccate the fat. This solution has been validated for the use in radical cystectomy specimens and enhances node yield and identification of smaller nodes.[9] After 6 hours in the solution, perivesical tissue dissection was performed with a board-certified pathologist, Figure 1C and 1D. To ensure meticulous inspection of perivesical fat, dissection was performed in 2 mm slices. At the conclusion of perivesical tissue dissection, the bladders were incised and grossly inspected to confirm the absence of occult bladder pathology and confirm there was no unexamined perivesical tissue. Perivesical lymph node size and location in relation to bladder wall were recorded. Histologic examination of grossly identified specimens was performed utilizing hematoxylin and eosin staining to evaluate for lymphoid tissue. A lymph node was defined as any tissue with histologically confirmed lymphoid tissue.

Results

The average cadaver age at expiration was 71.8 (range 59-95) and body mass index (BMI) was 21.0 kg/m^2 (range 13.6-27.5). During dissection, intrabdominal or pelvic pathology was not identified in any of the cadavers. Additionally, gross inspection of the bladder wall and urothelium did not demonstrate the presence of occult bladder pathology in any of the specimens.

Figure 2 provides an illustration of the proposed perivesical regions. Eight anatomic locations for perivesical nodes were developed. These include urachal, anterior bladder wall, posterior peritoneum, bladder neck, bilateral pedicle, bilateral lateral bladder wall. Figure 1 also shows inking of these proposed regions on radical cystectomy specimens.

Table 1 demonstrates the distribution of lymph nodes, both by gross and microscopic evaluation. Overall, gross tissue resembling perivesical lymph nodes were identified in 50% (3/6) of the cadavers. There were a total of six grossly-identified lymph nodes. The mean lymph node size was 7.5 mm (2-16 mm). The mean distance from bladder wall was 9 mm and all lymph nodes were within 15 mm of the bladder wall (3-15 mm). On histologic analysis, 4 of the 6 (66%) grossly identified lymph nodes had confirmed lymphoid tissue.

Discussion

This anatomic study confirms the presence of perivesical lymph nodes in radical cystectomy specimens. Gross tissue appearing like perivesical lymph nodes were identified in a 3 out of 6 the specimens. However, histologically-confirmed lymph nodes were found in 66% of gross lymph node specimens. In an effort to obtain precise knowledge about the pattern of lymphatic tumor spread, Leissner and colleagues conducted a prospective analysis of lymph node metastasis in bladder cancer patients

undergoing cystectomy with extended lymph node dissections.[10] In their study, the authors reported the presence of perivesical nodes in 14% (41/290) specimens. However, perivesical node assessment was not a primary endpoint of this study and subsequently perivesical node mapping was not performed. Additionally, there was no standardized definition of what constituted a perivesical lymph node in this study.

The discrepancy between the gross and histologically-confirmed lymph nodes reflects the difficulty in lymph node identification, both in the research and clinical setting. Studies to date have primarily relied upon gross palpation to identify and define a pelvic lymph node.[11,12] We elected to utilize microscopic evaluation for lymphoid tissue for two main reasons. The first is for superior accuracy, especially since this is the first detailed analysis of the perivesical space for lymph nodes, to the best of our knowledge. The second is that putative perivesical lymph nodes are surrounded by more fat than other pelvic nodes. We have chosen to report both the gross and microscopically-identified lymph node tissue given that there may have been a similar discrepancy in prior studies and that our concordance rate could be used in future studies.

The clinical significance of perivesical lymph nodes in radical cystectomy has been previously investigated. Bella et al determined positive perivesical lymph node disease was an independent predictor of worse overall survival.[13] A retrospective study by Hu et al reviewed 2,017 patients who underwent radical cystectomy with pelvic lymphadenectomy for curative intent for urothelial carcinoma.[7] Patients were classified according to lymph node status including positivity of perivesical nodes at pathologic examination. The combination of positive perivesical lymph node disease with positive pelvic lymph node disease was associated with worse survival, even when accounting for the number of positive lymph nodes. Interestingly, 47% of patients had identified perivesical lymph nodes in this study, compared 50% in our study. A recent retrospective study investigating the prognostic implication of isolated perivesical lymph node metastasis demonstrated significantly worse cancer specific survival for perivesical lymph node positive patients and no identifiable pelvic lymph node disease.[14] Another retrospective review determined the presence of positive perivesical lymph nodes carry similar prognostic implications as positive pelvic nodes found during standard lymphadenectomy.[15] These studies suggest the importance of evaluating the perivesical lymph nodes for metastatic disease, as patients would be inappropriately understaged on final pathology if a standard lymphadenectomy was only performed.

Lymph node counts vary depending on pathologic processing. This is evidenced by significant variations between institutions and even with the same surgeon.[16] The surgeon's resection of lymph nodes in separate packets has also been shown to increase lymph node counts.[12,17] Prior to histological evaluation, the anatomic grossing protocol is important for identification of perivesical lymph nodes. Some surgical pathology dissection textbooks describe palpating for perivesical lymph nodes and sectioning if any suspicious tissue is present.[18] Additional textbooks advise less intense evaluation of the cystectomy specimen, recommending sectioning perivesical lymph nodes only if nodes are grossly present.[19-21] Others have described making parallel incisions on the cystectomy specimen prior to palpation to help with gross identification.[19] Taking into account the limitations of prior studies, our cadaveric analysis provides the most detailed assessment of the perivesical tissue to help overcome the obstacles of perivesical fat, small lymph nodes (< 5 mm), and a primary specimen analysis that is typically focused on the bladder tumor.

Our study argues for a more thorough evaluation of the cystectomy specimen for perivesical lymph nodes. A more thorough evaluation of the perivesical specimen may identify no lymph nodes, lymph nodes without cancer, or lymph nodes positive for cancer. Identifying more normal lymph nodes likely would have no impact upon patient prognosis, but would improve confidence in confirming pathologically organ-confined disease, and reflect the quality of lymphadenectomy by increasing lymph node yield. The important potential implication for this study is in identifying occult perivesical nodal disease. Whether isolated or in combination with other positive lymph nodes, this more accurate pathologic staging would be critical in prognostication and risk stratification, and delineates which patients would benefit from more rigorous surveillance protocols or adjuvant therapies.

While our study's strength was the ability to perform a meticulous dissection of all areas of tissue, it was limited in the number of bladder specimens able to be evaluated. One reason for this limitation was the prioritization of using only un-embalmed cadavers. While associated with higher costs and a different procurement process, these cadavers allow for maintained surgical planes and tissue integrity very similar to those encountered at the time of surgery. A detailed anatomic analysis with embalmed cadavers would likely not allow for the same accuracy. As the

first detailed anatomic study on perivesical lymph nodes, this study prioritized the accuracy of the tissue dissection. However, due to the limited number of cadavers, extrapolating the exact clinical relevance or drawing firm conclusions about perivesical lymph nodes on a population basis should not be made. Ideally, formal mapping studies with more patients and clinical endpoints would help determine the significance of perivesical lymph nodes.

Despite these limitations, this study establishes a foundation upon which future clinical studies can evaluate perivesical lymph nodes. By describing perivesical regions and identifying higher-yield locations (pedicle, lateral bladder wall), future studies can be better targeted with an emphasis on these locations. If replicated in the clinical setting, changes in the grossing and evaluation of the cystectomy specimens may be necessary.

Conclusion

This cadaveric study with meticulous dissection of the perivesical space confirms that perivesical lymph nodes are a distinct entity and separate from other lymph nodes in the true pelvis. Perivesical lymph nodes are not present in all subjects and pathologic evaluation for perivesical lymph nodes is more difficult owing to the surrounding fat. We herein propose regions for evaluating the perivesical regions which can serve as a foundation for future studies and anatomic grossing techniques. □

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